

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

Serial No. 10/030,186

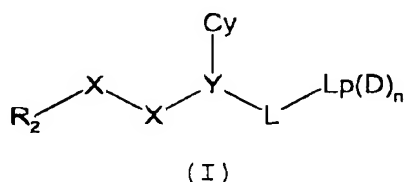
Response to Office communication of October 29, 2003

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1 (currently amended): A serine protease inhibitor compound of formula (I)



wherein:

~~R<sub>2</sub> is: a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, MeSO<sub>2</sub> or R<sub>1</sub>, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio~~

(i) phenyl optionally being substituted in the 3 and/or 4 position by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy,

Serial No. 10/030,186

Response to Office communication of October 29, 2003

MeSO<sub>2</sub>- or R<sub>1</sub>, and optionally substituted at the 6 position by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(ii) naphth-2-yl optionally substituted at the 6 or 7 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub> and optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>;

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

(ix) pyrid-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

(x) pyrid-3-yl optionally substituted at the 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

(xi) benzofur-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano,



Serial No. 10/030,186

Response to Office communication of October 29, 2003

~~acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;~~

~~R<sub>1</sub> is as defined for R<sub>1a</sub>, provided that R<sub>1</sub> is not unsubstituted aminoalkyl;~~

Y (the  $\alpha$ -atom) is ~~CH<sub>a</sub> nitrogen atom or a CR<sub>1b</sub> group;~~

Cy is an optionally R<sub>3a</sub> substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinoloyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by R<sub>3i</sub>X<sub>i</sub> in which X<sub>i</sub> is a bond, O, NH or CH<sub>2</sub> and R<sub>3i</sub> is phenyl, pyridyl or pyrimidinyl optionally substituted by R<sub>3a</sub> ~~saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R<sub>3a</sub> or phenyl optionally substituted by R<sub>3a</sub> or R<sub>3i</sub>X<sub>i</sub>;~~

each R<sub>3a</sub> independently is hydrogen; hydroxyl; alkoxy; alkyl; alkylaminoalkyl; hydroxymethyl; carboxy; alkoxyalkyl; alkoxycarbonyl; alkylaminocarbonyl; aminomethyl; CONH<sub>2</sub>; CH<sub>2</sub>CONH<sub>2</sub>; (1-6C)alkanoylamino; alkoxycarbonylamino; amino; halo; cyano; nitro; thiol; alkylthio; alkylsulphonyl; alkylsulphenyl; alkylsulphonamido; alkylaminosulphonyl; aminosulphonyl; haloalkoxy; haloalkyl; a group of the formula -C(X<sup>3</sup>)N(R<sup>11</sup>)R<sup>12</sup> (wherein X<sup>3</sup> is O or S and R<sup>11</sup> and R<sup>12</sup> are independently selected from hydrogen, methyl, ethyl, or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group; or -OCH<sub>2</sub>O- which is bonded to two adjacent ring atoms in CyR<sub>1e</sub>er ~~amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphenyl, alkylsulphonyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkylloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphenyl,~~

Serial No. 10/030,186

Response to Office communication of October 29, 2003

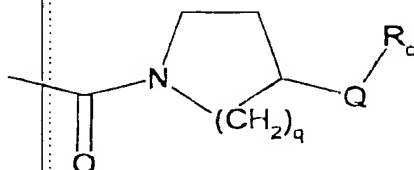
~~aminosulphenyl, haloalkoxy, haloalkyl, a group of the formula~~  
 ~~$C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S, and  $R^{11}$  and  $R^{12}$  are~~  
~~independently selected from hydrogen, methyl or ethyl or~~  
~~together with the nitrogen atom to which they are attached~~  
~~form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group),~~  
~~or  $OCH_2O$  which is bonded to two adjacent ring atoms in Cy;~~

~~$X_1$  is a bond, O, NH or  $CH_2$ ;~~

~~$R_{3j}$  is phenyl, pyridyl or pyrimidinyl optionally~~  
~~substituted by  $R_{3a}$ ;~~

~~$R_{1b}$ ,  $R_{1c}$  and  $R_{1j}$  are as defined for  $R_{1a}$ ;~~ and

~~-L-Lp(D)<sub>n</sub> is~~



$q$  is 1 or 2;

$Q$  is methylene; and  $R_q$  is  $NR_aR_b$  in which each of  $R_a$  and  $R_b$  independently is hydrogen or  $C_{1-3}$ alkyl; or one of  $R_a$  and  $R_b$  is hydrogen or methyl and the other of  $R_a$  and  $R_b$  is (3-6C)cycloalkyl, pyrid-4-yl,  $-CH_2-R_c$  or  $-CH_2-R_d$  in which  $R_c$  is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl,  $CONH_2$ ,  $SO_2NH_2$ , methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which  $R_d$  is isopropyl or cyclopentyl, or  $NR_aR_b$  is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino [in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino may be optionally substituted on a ring carbon atom by hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy,

Serial No. 10/030,186

Response to Office communication of October 29, 2003

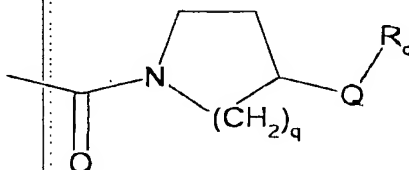
methoxycarbonyl or ethoxycarbonyl (provided that the amino, hydroxy or alkoxy substituent is not on a ring carbon atom which is included in a double bond, or adjacent to a ring oxygen, sulfur or nitrogen atom) and in which the piperazino or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position];

or a physiologically-tolerable salt thereof.

2 (currently amended): A compound according to claim 1 wherein

Cy is an optionally R<sub>3a</sub> substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group;  
each R<sub>3a</sub> is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, CONH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub>, acetyl amino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl;

-L-Lp(D)<sub>n</sub> is of the formula:



wherein:

q is 1 or 2;

Q is methylene; and R<sub>q</sub> is NR<sub>a</sub>R<sub>b</sub> in which each of R<sub>a</sub> and R<sub>b</sub> independently is hydrogen or C<sub>1</sub>-3alkyl; or one of R<sub>a</sub> and R<sub>b</sub> is hydrogen or methyl and the other of R<sub>a</sub> and R<sub>b</sub> is -CH<sub>2</sub>-R<sub>c</sub>

Serial No. 10/030,186

Response to Office communication of October 29, 2003

or-CH<sub>2</sub>-R<sub>d</sub> in which R<sub>c</sub> is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, CONH<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which R<sub>d</sub> is isopropyl or cyclopentyl, or NR<sub>a</sub>R<sub>b</sub> is pyrrolidino, piperidino, morpholino, piperazino, or tetrahydro-1,4-diazepino in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a pyrrolidino, piperidino, piperazino, or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position; or a physiologically-tolerable salt thereof.

3 (previously presented): A compound according to claim 1 wherein q is 2.

4 (previously presented): A compound according to claim 1 wherein R<sub>q</sub> is NR<sub>a</sub>R<sub>b</sub> in which R<sub>a</sub> is hydrogen or C<sub>1</sub>-3alkyl and R<sub>b</sub> is C<sub>1</sub>-3alkyl; or R<sub>a</sub> is hydrogen and R<sub>b</sub> is (3-6C)cycloalkyl or pyrid-4-yl; or NR<sub>a</sub>R<sub>b</sub> is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino [in which a pyrrolidino, piperidino or piperazino may be optionally substituted on a ring carbon atom by hydroxy or hydroxymethyl (provided that the hydroxy substituent is not on a ring carbon atom which is adjacent to a ring nitrogen atom) and in which the piperazino may bear a methyl group at the 4-position].

5 (previously presented): A compound according to claim 1 wherein R<sub>q</sub> is selected from dimethylamino, diethylamino, prop-2-ylamino, pyrrolidino, 3-pyrrolino, 3-hydroxypyrrolidino, 3-hydroxymethylpyrrolidino, piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 4-hydroxymethylpiperidino, piperazino and 4-methylpiperazino.



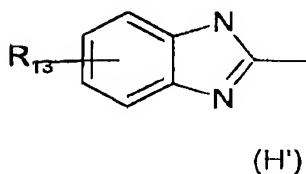
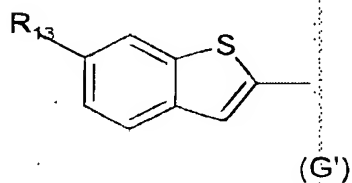
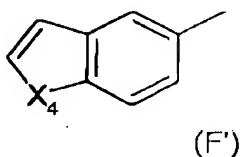
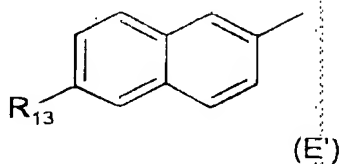
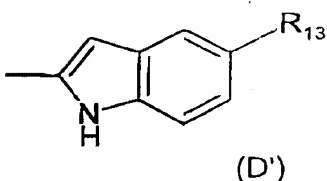
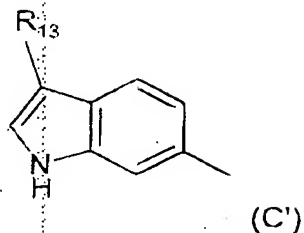
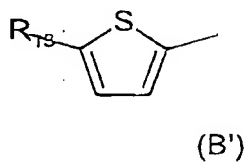
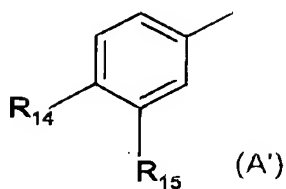
Serial No. 10/030,186

Response to Office communication of October 29, 2003

6 (canceled):

7 (canceled):

8 (previously presented): A compound according to claim 1 wherein  $R_2$  is selected from one of the formula (A') to (H'):



wherein  $X_4$  is O or S,  $R_{13}$  is selected from hydrogen, chloro or methyl and  $R_{14}$  is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and  $R_{15}$  is selected from hydrogen, methyl, fluoro, chloro and amino.

Serial No. 10/030,186

Response to Office communication of October 29, 2003

9 (original): A compound according to claim 8, wherein R<sub>2</sub> is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

10 (canceled):

11 (canceled):

12 (canceled):

13 (canceled):

14 (canceled):

15 (canceled):

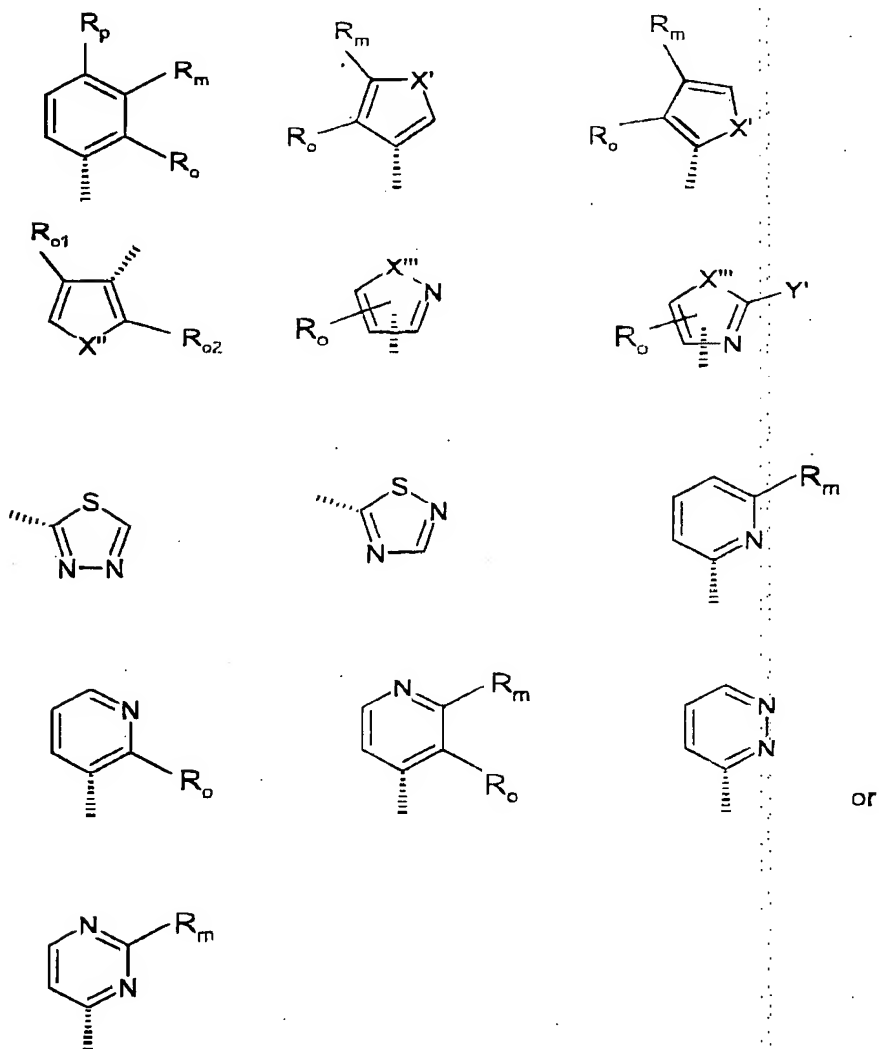
16 (currently amended): A compound according to claim ~~12-1~~ wherein R<sub>3a</sub> is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, CONH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub>, acetyl amino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl or morpholin-1-ylcarbonyl and -OCH<sub>2</sub>O- (which is bonded to two adjacent ring atoms in Cy).

17 (canceled):

Serial No. 10/030,186

Response to Office communication of October 29, 2003

18 (previously presented): A compound according to claim 1  
wherein Cy is selected from:



wherein:

$X'$  is selected from O, S and NMe;

$X''$  is selected from O and S;

$X'''$  is selected from O, S, NH and NMe;

$Y'$  is selected from hydrogen, amino and methyl;

Serial No. 10/030,186

Response to Office communication of October 29, 2003

$R_O$  is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;

$R_m$  is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula  $-C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S, and  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

$R_P$  is selected from hydrogen and fluoro; or

$R_O$  and  $R_m$  or  $R_m$  and  $R_P$  form an  $-OCH_2O-$  group; or

$R_O$  and  $R_m$  together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroaryl ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and

one of  $R_{O1}$  and  $R_{O2}$  is hydrogen and the other is  $R_O$ .

19 (previously presented): A compound according to claim 18 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naphth-1-yl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

20 (currently amended): A compound as claimed in any one of Claims 1 to 5, 8 to 9, 16 and 18 to 19, in which the alpha atom in Y is ~~carbon and~~ has the conformation that would result from construction from a D- $\alpha$ -aminoacid  $NH_2-CH(Cy)-COOH$   $NH_2-CH(Cy)-COOH$  where the  $NH_2$  represents part of X-X.

Serial No. 10/030,186

Response to Office communication of October 29, 2003

21 (previously presented) A pharmaceutical composition, which comprises a compound as claimed in claim 1 together with at least one pharmaceutically acceptable carrier or excipient.

22 (canceled):

23 (canceled):

24 (currently amended): A method of treatment of a human or non-human animal body to combat a thrombotic disorder selected from venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, myocardial infarction and cerebral thrombosis, which comprises administering to said body an effective amount of a compound as claimed in claim 1.

25 (canceled):

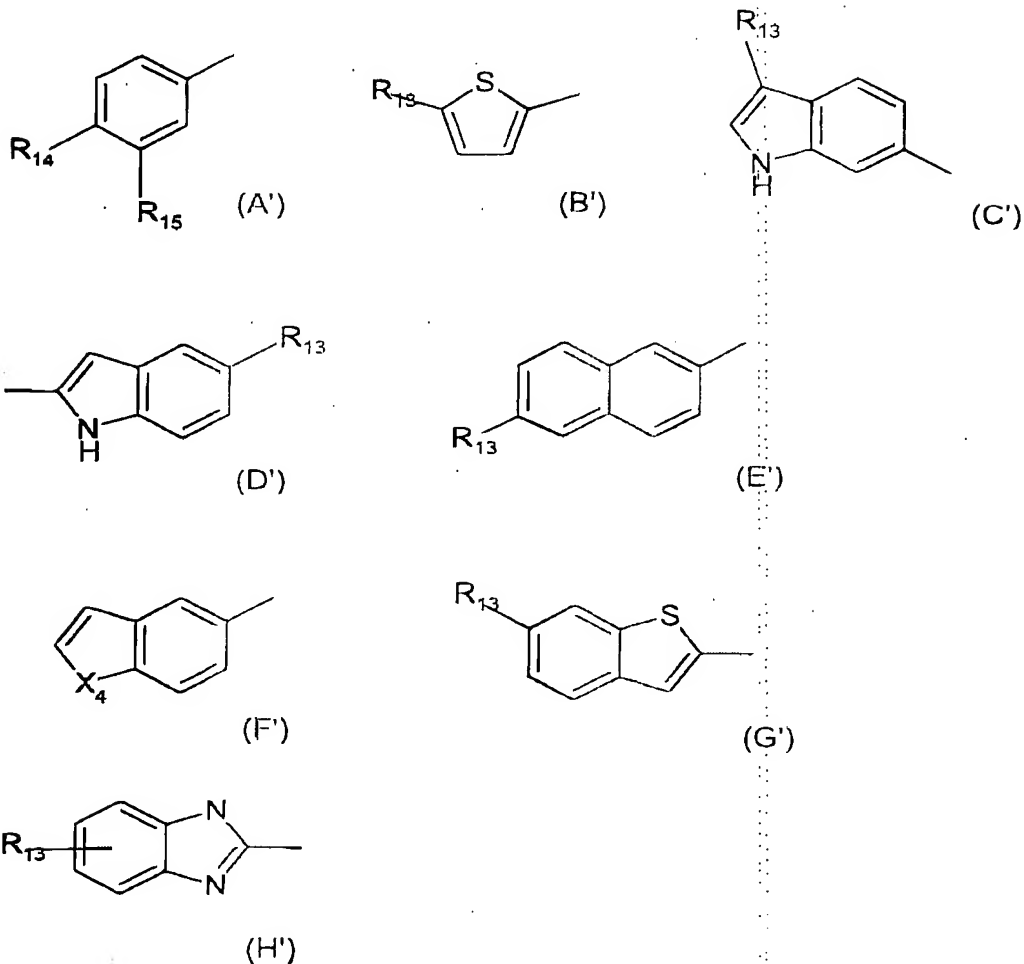
26 (canceled):

27 (currently amended) A compound according to claim 1 wherein:-

R<sub>2</sub> is selected from one of the formula (A') to (H'):

Serial No. 10/030,186

Response to Office communication of October 29, 2003



wherein  $X_4$  is O or S,  $R_{13}$  is selected from hydrogen, chloro or methyl and  $R_{14}$  is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and  $R_{15}$  is selected from hydrogen, methyl, fluoro, chloro and amino;

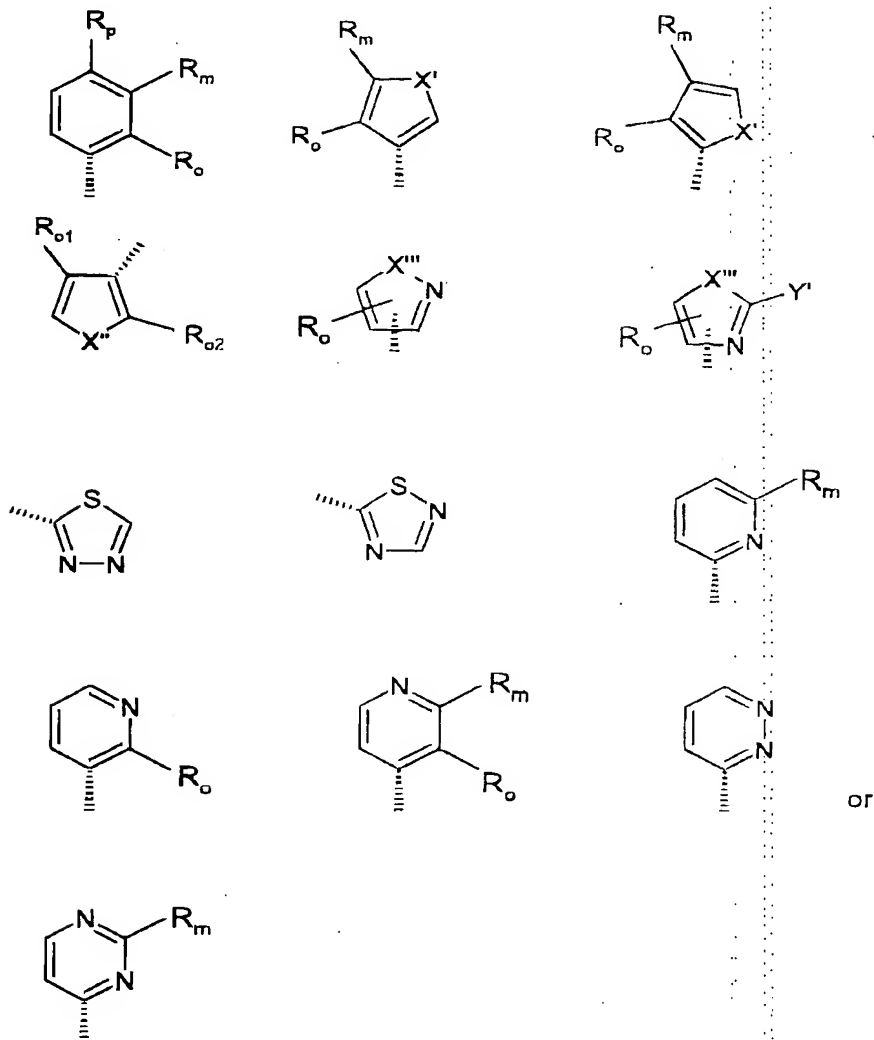
-X-X- is -CONH-;

Y is CH and has the conformation that would result from construction from a D- $\alpha$ -aminoacid  $\text{NH}_2\text{-CH}(\text{Cy})\text{-COOH}$   $\text{NH}_2\text{-CH}(\text{Cy})\text{-COOH}$  where the  $\text{NH}_2$  represents part of X-X;

Cy is selected from

Serial No. 10/030,186

Response to Office communication of October 29, 2003



wherein:

 $X'$  is selected from O, S and NMe; $X''$  is selected from O and S; $X'''$  is selected from O, S, NH and NMe; $Y'$  is selected from hydrogen, amino and methyl; $R_o$  is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl; $R_m$  is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl,

Serial No. 10/030,186

Response to Office communication of October 29, 2003

methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula  $-C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S, and  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);  $R_p$  is selected from hydrogen and fluoro; or  $R_o$  and  $R_m$  or  $R_m$  and  $R_p$  form an  $-OCH_2O-$  group; or  $R_o$  and  $R_m$  together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroaryl ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and one of  $R_{o1}$  and  $R_{o2}$  is hydrogen and the other is  $R_o$ ; and  $q$  is 2.

28 (previously presented): A compound according to claim 27 wherein  $R_q$  is selected from dimethylamino, diethylamino, prop-2-ylamino, pyrrolidino, 3-pyrrolino, 3-hydroxypyrrolidino, 3-hydroxymethylpyrrolidino, piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 4-hydroxymethylpiperidino, piperazino and 4-methylpiperazino.

29 (previously presented): A compound according to Claim 28 wherein  $R_2$  is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

30 (previously presented): A compound according to claim 29 wherein  $C_y$  is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naphth-1-yl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.



Serial No. 10/030,186

Response to Office communication of October 29, 2003

31 (previously presented) A compound according to claim 30  
wherein Cy is phenyl.